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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/067,741	02/08/2002	Katherine Galvin	MPI95-001CP1CP1CNIM	9620

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EXAMINER	
FALK, ANNE MARIE	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 04/19/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/067,741	GALVIN ET AL.	
	Examiner	Art Unit	
	Anne-Marie Falk, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 February 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-9 and 26-28* is/are pending in the application.

4a) Of the above claim(s) _____. is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-9 and 26-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 February 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/12/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed February 4, 2005 has been entered. Claims 1 and 26 have been amended. Claims 5 and 10-13 have been cancelled.

Accordingly, Claims 1-4, 6-9, and 26-28 remain pending in the instant application.

The remarks filed October 15, 2004 (herein after referred to as "the response") are considered herein.

The objection to the specification is withdrawn in view of the amendment to the abstract.

The rejection of Claims 1-4 under 35 U.S.C. 101 is withdrawn in view of the amendments to Claims 1 and 26 to add the term "nonhuman."

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-4, 6-9, and 26-28 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1-11 of U.S. Patent No. 6,359,194. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims encompass the same transgenic animals, as well as cells isolated therefrom, and methods of making and using the same transgenic animals, particularly a mouse. The transgenic animals as claimed in the instant application embrace the genus of 'animals,' while the claims of U.S. Patent No. 6,359,194 are directed to a species of animal, i.e. a mouse. Therfore, the claims directed to the transgenic mouse anticipate the claims directed to transgenic animals.

At page 10 of the response, Applicants state that they will file a Terminal Disclaimer if conflicting claims are indicated as being otherwise allowable. Accordingly, the double patenting rejection will be held in abeyance until a conflicting claim is free of other rejections.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 6-9, and 26-28 stand rejected under 35 U.S.C. 112, first paragraph, for reasons of record set forth in the previous Office Action (mailed 9/22/03), because the specification, while being enabling for a homozygous transgenic mouse whose germ cells comprise a mutated rchd534-LacZ gene which lacks the MH2 domain-encoding region, wherein the endogenous wild-type rchd534 gene of said mouse has been replaced with said mutated rchd534-LacZ gene which lacks the MH2 domain-encoding region, and wherein said mouse displays a cardiovascular disease symptom as follows: hyperplasia, thickening of at least one cardiac valve, cardiac outflow tract development defects, cardiovascular calcification, epicardial vascular malformations, endocardial vascular malformation, or defects in the

regulation of vascular tone, and methods of making and using the same, does not reasonably provide enablement for all other transgenic animals embraced by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with the scope of the claims.

The claims are directed to a homozygous transgenic animal having a mutated rchd534 gene, wherein the wild-type rchd534 gene has been replaced with a rchd534-LacZ gene, which lacks the MH2 domain coding region, and wherein said animal displays a cardiovascular disease symptom. The claims are further directed to cells isolated from the transgenic animals and methods of using the transgenic animals.

At page 6, paragraph 2 of the response, Applicants assert that they have taught how one of skill in the art can generate transgenic animals, characterize the animals for expression or lack of expression of the gene of interest and perform phenotypic analysis and breeding. Applicants point to pages 40-44 of the specification for providing these teachings. Applicants further assert that they have taught that "rats, rabbits, guinea pigs, pigs, micro-pigs, goats and non-human primates, may be used to generate cardiovascular disease animal models" at page 41, lines 14-16. On the contrary, while the specification contemplates that knockout animals can be made for species other than mice, there are no teachings that provide the necessary guidance for making knockout rats, rabbits, guinea pigs, pigs, micro-pigs, goats and non-human primates. Applicants further assert that "Applicants disclose the various techniques, which were known in the art at the time of filing, to introduce a target gene transgene into animals to produce the founder lines of transgenic animals. The techniques described include, for example, pronuclear microinjection, retrovirus mediated gene transfer into germ lines, gene targeting in embryonic stem cells, electroporation of embryos and sperm-mediated gene transfer" (page 6, paragraph 2 of the response). Applicants arguments are inapposite because these techniques **cannot be used to produce targeted gene replacements.** The claims explicitly require a targeted gene replacement. See Claim 1 which explicitly recites "wherein the wild-type rchd534 gene has been replaced with the mutated rchd534 gene." The

specification does not teach how to use pronuclear microinjection, retrovirus-mediated gene transfer, electroporation, or sperm-mediated gene transfer to produce a **targeted gene replacement.** Likewise, the prior art does not teach how to use these gene transfer techniques to produce targeted gene replacement in an animal's germline. The prior art only teaches how to make germline targeted gene replacements in a **mouse** by gene targeting techniques using embryonic stem (ES) cells. Since ES cells are required to produce germline targeted gene replacements, and only mouse ES cells were available in the prior art, as evidenced by the cited prior art made of record in the previous Office Action, the skilled artisan would not have been able to make the claimed transgenic animal in any species other than a mouse. Thus, as set forth in the previous Office Action, transgenic knockout technology is limited to the mouse system.

At page 6, paragraph 2 of the response, Applicants point to page 43, lines 1-16 of the specification and assert that "Applicants further describe various breeding methods that would enable one of skill in the art to obtain the type of transgenic line desired." Contrary to Applicants' assertion, nowhere does the specification or the prior art teach how breeding methods can be used to obtain a **targeted gene replacement.**

At page 7, paragraph 1 of the response, Applicants point to the references of Murray et al. (1989), Clements et al. (1994), Janne et al. (1992), and Ebert et al. (1991) for teaching transgenic sheep, goats, and cows. However, none of these references are directed to knockout technology or methodology for producing a targeted gene replacement. No sheep, goat, or cow carrying a **targeted gene replacement** is described in any of these references. References describing transgenic animals that have a transgene randomly integrated into the animal's genome do not pertain to the instantly claimed invention, as the instantly claimed invention requires targeted integration, not random integration.

At page 8, paragraph 2 of the response, Applicants again refer to the publications of Murray et al. (1989), Clements et al. (1994), Janne et al. (1992), and Ebert et al. (1991) for teaching transgenic sheep, goats, and cows. The assertions relating thereto are addressed in the preceding paragraph. Applicants further cite Powell et al. (1994) for teaching the production of a transgenic sheep. Again, this reference

does not relate to knockout technology or methodology for producing a targeted gene replacement. Powell et al. does not describe a transgenic sheep carrying a **targeted gene replacement**, as is required for the instantly claimed invention. References describing transgenic animals that have a transgene randomly integrated into the animal's genome do not pertain to the instantly claimed invention, as the instantly claimed invention requires **targeted** integration, not random integration.

At page 8, paragraph 2 of the response, Applicants assert that "[t]he concept of using animals as bioproducers of therapeutic proteins by generating transgenic animals was developed prior to the filing of the instant application." Applicants point to the production of various transgenic animals producing therapeutic proteins in their milk, particularly the human a1-antitrypsin transgenic sheep. However, the instantly claimed invention does not relate to the production of bioreactor-type transgenic animals. Quite the contrary, the instantly claimed invention is directed to transgenic animals that have **lost** the ability to express their **endogenous** rchd534 protein. Such animals are known as **knockout** animals and are quite distinct from bioreactor transgenic animals that express an **exogenous** protein under the direction of a mammary specific promoter. Likewise, the techniques for making knockout animals differ substantially from the techniques established for generating transgenic animals that overexpress an exogenous protein.

In view of the lack of guidance provided in the specification relating to the production of targeted gene replacements in animals other than mice, the absence of working examples relating to animals other than mice, the broad scope of the claims, the unpredictability in the art, the undeveloped state of the art for making targeted gene replacements in animals other than mice, and the substantial quantity of experimentation necessary to enable the claimed invention over the full scope of animals, undue experimentation would have been required for the skilled artisan to practice the claimed invention over the full scope.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4, 6-9, and 26-28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-4, 6-9, and 26-28 are indefinite in their recitation of "the mutated rchd534 gene is a rchd534-LacZ gene which lacks the MH2 domain encoding region" because the term "rchd534-Lacz gene" is not defined in the specification and therefore the arrangement of the targeting construct need not produce an inactive allele, although the specification teaches that loss of expression of the rchd534 protein correlates with the observed phenotype.

Conclusion

No claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling

please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (571) 272-0728. The examiner can normally be reached Monday through Friday from 10:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735. The central official fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Anne-Marie Falk, Ph.D.

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER